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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,764	10/24/2003	Stuart B. Levy	16534-539001US	8952

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EXAMINER	
EPPS SMITH, JANET L	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
05/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,764	LEVY ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Smith	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,37-47,54 and 57-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 37-47, 54 and 57-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-03-2009 has been entered.

Response to Amendment

2. The instant specification was previously given a priority date of 10/24/2002, however since Applicants have amended the claims to recite limitations that do not find support in the specification as originally filed, the instant claims are given a priority date as of the filing date of the current amendment to claims, 3-02-2009.

3. Applicant's amendment to the claims to include the limitation "spinal muscular atrophy," is an improper incorporation by reference since according to Applicants support for this limitation was found "for example, on pages 240-241 of Philips et al. (2000), Cell. Mol. Life Sci., 57:235-249 and on page 21 of Stoss et al, (2000), Gene Ther. Mol. Biol. 5:9-30 (courtesy copies enclosed), each of which is expressly incorporated by reference in the instant specification on page 9, lines 14-17 and lines 28-29 and page 102, lines 14-16 of the specification."

4. However, the material introduced into the claims is considered to be essential material, necessary to provide a written description of the claimed invention, therefore

incorporation of this material based upon the disclosure of a non-patent literature publication incorporated by reference is improper as per 37 CFR 1.57(c) as set forth below:

> c) "Essential material" may be incorporated by reference, but only by way of incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. "Essential material" is material that is necessary to:
>
> (1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of 35 U.S.C. 112;
>
> (2) Describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by the second paragraph of 35 U.S.C. 112; or
>
> (3) Describe the structure, material, or acts that correspond to a claimed means or step for performing a specified function as required by the sixth paragraph of 35 U.S.C. 112.

5. The amendments filed on 11/05/07 are acknowledged. Applicants have cancelled claims 2-6, 8, 10-11. Applicants have added new claims 58-64. Thus currently, claims 1, 37-47, 54 and 57-64 are pending and under examination.

6. In the previous office action the following rejections were made, however all of the following rejections are withdrawn in response to Applicant's amendment to the claims to recite wherein the disease :

- Claims 1, 37-47 were rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims in EACH of U.S. Patent Nos. 6,500,812-claim 15, 6,624,168-claim 6, 6,642,270, 6,683,068, 6,818,634, 6,818,635, 6,833,365, 6,846,939, 6,849,615,7,045,507, and 7,094,806.

- Claims 1, 37-47 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application Nos. 10/692,563, 10/752,378, 10/786,881, 10/943,571.

- Claims 1, 2, 8, 10, 11, 36-38 were rejected under 35 U.S.C. 102(b) as being taught by Yrjanheikki et al (Tetracyclines Inhibit Microglial Activation and are Neuroprotective in Global Brain Ischemia. PNAS, 1998.95:15769-15574).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,500,812).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,624,168).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,642,270).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,683,068).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,818,634).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,818,635).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,846,939).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,849,615).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Draper et al (US Patent No. 7,045,507).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 7,094,806).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 7,202,235).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Draper et al (US Patent Publication No. US 20040242548).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Huss et al (US Patent Publication No. US 20040266740).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent Publication No. US 20050026876).

- Claims 1, 37-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Draper et al (US Patent Publication No. US 20050070510).

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. The following rejections were maintained or necessitated by applicant's amendments. Applicants have amended the claims to recite "wherein said DTMR associated with splicing of nuclear RNA is spinal muscular atrophy," which was not a limitation in any previously presented claims.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 36-47, 54, 57, 59-60, 62-64 remain and claim 65 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons of record and those set forth below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

11. The instant claims are drawn to a method for treating a Disease Treatable by Modulation of RNA (DTMR) associated with splicing of nuclear RNA, comprising: administering to said subject an effective amount of a tetracycline compound of formula

(I) to modulate splicing, wherein said DTMR associated with splicing of nuclear RNA is spinal muscular atrophy.

12. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter., 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

1) The nature of the invention. The invention involves a method of treating Spinal Muscular Atrophy (SMA) comprising the administration of *any* species of tetracycline derivative compound that falls within the scope of formula (I) as recited in the instant claims, wherein the compound is administered in an "effective amount" to modulate (i.e. increase, decreases, or etc.) the nuclear RNA splicing of an undefined gene target that is associated with Spinal Muscular Atrophy in any subject. The scope of the claimed method involves the modulation of subject's nuclear RNA splicing of an undefined mRNA target in the subject, including activation of cryptic splice sites, silencing of splice sites, silencing of exonic or intronic splicing enhancers, silencing of exonic or intronic splicing silencers, the alteration of the binding or component of the splicing machinery to the RNA, or affecting the intermolecular interactions between components of the splicing machinery. Furthermore, the method reads on treating humans.

2) Number of working examples. Applicants have provided multiple examples of making different tetracycline derivate compounds (see examples 1-2). Applicant's have provided a single example of the treatment of two independent murine macrophage cells lines (J774.2 and RAW 264.7) in which there is up-regulation or down regulation of mRNA as assed by microarray technology (see example 3). There is no disclosure if these murine macrophage cells are an art accepted model for a particular DTMR associated with splicing. Example 4 investigates the *in vitro* cytotoxicity of two tetracycline compound derivatives (minocycline and doxycycline) on Cos-1 and CHO-K1 cells and Example 5 investigates the *in vitro* anti-bacterial activity of 2 undisclosed tetracycline derivative compounds. There is no disclosure of an *in vivo* treatment of a particular DTMR associated with splicing in a working example. Moreover, there is no specific guidance set forth in the specification as filed regarding how to use the broad genus of compounds encompassed by formula (I) for the treatment of SMA. There is no disclosure in Example 3 of how the modulation of RNA occurs (translation, half-life, translocation, protein binding, or splicing) is effected by the exposure to the tetracycline derivatives. Applicant's do not disclose which particular genes are up-regulated or down regulated, but simply disclose the total up-regulated or down-regulated genes in table 3 (page 116 of the instant specification). There is no disclosure if the modulation of RNA splicing results in any protein modulation or in the amelioration of symptoms of SMA.

3) Amount of direction or guidance present. The applicants provide very generic teaching of methods of treating a subject for a DTMR. The specification teaches that a DTMR associated with splicing includes:

Other exemplary DTMRs include disorders caused by, or associated with splicing. For example, some disorders associated with defects in pre-mRNA processing result from a loss of function due to mutations in regulatory elements of a gene. Examples of such mutations are described in Krawczak et al. (1992) Hum. Genet, 90:41- 54; and Nakai et al. (1994) Gene 14:171-177. Other DTMR include disorders which have been attributed to a change in trans-acting factors. Examples of DTMRs which are associated with splicing include those described in Philips et al. (2000), Cell. Mol. Life Sci., 57:235-249), as well as, FTDP- 17 (frontotemporal dementia with parkinsonism) and/β-thalassemia.
Certain DTMRs associated with splicing include those which are generated by point mutations that either destroy splice-sites or generate new cryptic sites in the vicinity of normally used exons. Examples of such DTMRs include cystic fibrosis (Friedman et al. (1999) Jr. Biol. Chem. 274:36193-36199), muscular dystrophy (Wilton et al. (1999) Neuromuscul. Disord. 9:330-338), and eosinophilic diseases (Karras et al., (2000) Mol. Pharamcol. 58:380-387).
Other DTMRs include cancers which may change splicing patterns during cancer formation and progression. Example of such cancers include, but are not limited to leukemia, colon/rectal cancer, myeloid leukemia, breast cancer; gastric carcinomas, acute leukemia, multiple myeloma, myeloid cell leukemia, lung cancer, prostate cancer, etc. Addition DTMRs associated with splicing are discussed in Stoss et al., (2000), Gene Ther. Mol. Biol. 5:9-30). (page 9, lines 8-29).

Applicant's single method step includes the "administering to said subject an effective amount of a tetracycline compound" but does not disclose how the single application of the tetracycline would differ from treating β-thalassemia, prostate cancer, or SMA. Although there is a brief reference to the Stoss et al. and Phillips et al. references in the specification as filed, there is no expressly stated reference to SMA in the disclosure as filed. Moreover, there are no specific guidelines set forth in the specification as filed or in the references incorporated by reference that would provide specific guidance how the ordinary skilled artisan would administer an effective amount

of the tetracycline compounds of the instant invention for the treatment of SMA. Additionally, applicants have not provided a clear nexus between the *in vitro* treatment of cells with the tetracycline compounds of the invention and the production of an *in vivo* effect in a human subject, i.e. the specific modulation of nuclear RNA splicing, and the production of a therapeutic result, the treatment (i.e. the amelioration) of symptoms of SMA.

Moreover, Applicants teach that the tetracycline compounds can be co-administered with a second agent "the second agent can be any agent which is known in the art to treat, prevent, or reduce the symptoms of a DTMR" including chemotherapeutic agents (page 93). Additionally, Applicants teach that the tetracycline compound can be administered as a pharmaceutical composition with a myriad of carriers, and methods of administration (page 94-9100). Applicants contend that the "effective amount" simply depends on size and weight of the subject, but then teaches that the choice of tetracycline compound can affect the "effective amount". Applicant's teaches, "[o]ne of ordinary skill in the art would be able to study the aforementioned factors and make the determination regarding the effective amount of the tetracycline compound without undue experimentation." Applicants further teach how actual dosages are determined by experimentation by the skilled artisan. However, applicant does not teach how to evaluate which tetracycline compounds have what effect on different diseases? Or how they modulate RNA splicing in different disease states? How would a skilled artisan decide between two different tetracycline derivatives?

Applicants disclose hundreds of specific tetracycline compounds (pages 16-79), and teaches the disclosure of thousands of derivatives of those compounds, including all tautomers thereof (page 92). However Applicants do not provide answers to the following: Do all tetracycline derivatives cause the exact same down-regulation or up-regulation of genes as those taught by applicant in example 3 in diseases associated with splicing? Are they all modulated to the same extent? Would the modulation of RNA splicing in murine macrophages be the same in human liver cells? Are there disease states where the down-regulation of those genes disclosed by applicant in example 3 would actually exacerbate the disease state rather than "treat" and therefore actually be contraindicative to treat that particular DTMR associated with splicing?

Applicant fails to disclose the particular genes that are modulated in Example 3, table 3, or furthermore do not recite which particular genes are modulated with respect to the treatment of SMA. What genes are these? Would the modulation, i.e. up-regulation or down regulation of these genes be detrimental in treating someone with SMA? Applicant does not teach any specifics, other than to suggest that the skilled artisan would know how to decipher between the hundreds of compounds disclosed in the specification.

The invention as claimed reads on a method of treating any subject, including animals, and humans, using any tetracycline compound for any disease state associated with spicing. There is no teaching in the specification of how to alter the method of treating one species of subject to another.

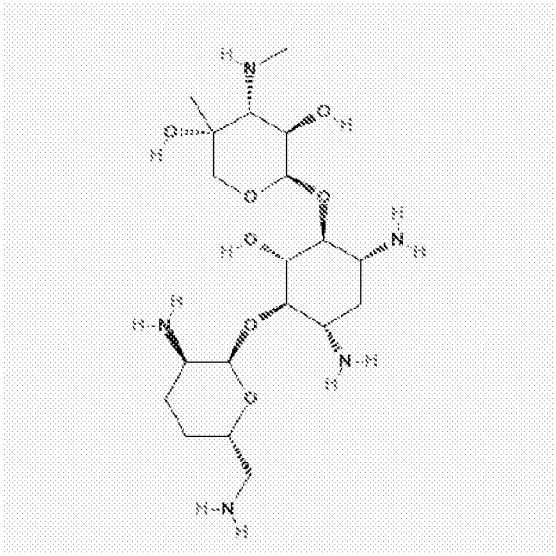
4) State of the art. The art shows that chemically modified tetracyclines are highly variable. Liu et al (The lipophilicity, Pharmacokinetics, and Cellular Uptake of Different Chemically-Modified Tetracyclines (CMTs). Current medicinal Chemistry, 2001. 8:243-252) teaches that CMTs have great therapeutic potential not as antibiotics, but as therapeutic agents for disease states (see introduction, page 243), and that at least one CMT used in his study was currently being tested to treat humans (page 251, last paragraph). Liu studies 9 different CMTs (Figure 1). Liu teaches that different CMTs have different properties which effect cellular uptake, clearance, and half-life of the CMT. These differences can be seen between *in vivo* studies compared to *in vitro* studies of the same CMT (page 243-244). Liu further teaches that the time for different CMTs to reach their peak maximum serum levels (C_{max}) and half-lives varied significantly (Page 248-249, Figure 3 and Table 1). Liu suggest that these ranges may be the result of poor absorption from the gastrointestinal tract, instability in the blood, rapid elimination from the serum (from urinary uptake, rapid detoxification or rapid tissue uptake), and that different organs showed different levels of uptake of the different CMTs (see page 249-250 and table 1). Liu further teaches that one CMT (CMT-7) tested was both unstable both in vitro and in vivo (page 250) and that the molecule was difficult to study because it is a tautomer and fluctuates between several forms (page 251). Liu stresses, "to asses the therapeutic potential of this series of compounds, their in vitro efficacy described above has to be "matched" to the pharmacokinetics, safety, and efficacy profile in vivo."

Hertweck et al (inhibition of nuclear pre-mRNA splicing by antibiotics in vitro. European Journal of Biochemistry, 2002. 269:175-183) teaches that a tetracycline derivative is capable of inhibiting splicing of nuclear pre-mRNA (see abstract). How would the skilled artisan know which tetracycline derivative is appropriate for which DTMR associated with splicing? Would it be improper to use a tetracycline derivate in a DTMR-associated with splicing, when the disease is caused by aberrant splicing, or would the inhibition of splicing lead to other diseases? What DTMR associated with diseases need to be treated by inhibiting splicing? What other tetracycline derivatives inhibit splicing?

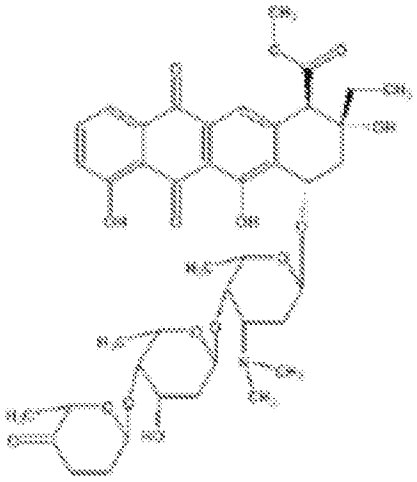
Chakkalakal et al (Molecular, cellular and pharmacological therapies for Duchenne/Becker muscular dystrophies. The FASEB Journal, 2005. 19(8):880-91) teaches that because some mutations known to cause DMD are due to the formation of a premature stop codon, one group studied using the antibiotic Gentamicin to cause suppression of stop codons, and there was some degree of restoration of muscle fibers. However, Chakkalakal reports that a second group trying to repeat the experiments was unsuccessful (see page 886, column I).

It is noted that the compounds of formula (I) recited in the instant claims are structurally distinct from Gentamicin.

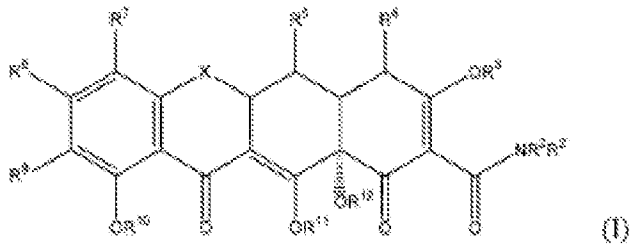
Gentamicin (structure from PubChem-NCBI) has the following structure:



Andreassi et al. teach that the administration of aclarubicin, a tetracycline related compound, for the restoration of SMN levels in cells derived from type I SMA patients. Aclarubicin has the following structure as compared to the tetracyclines of formula (I):



Aclarubicin



(I)

Formula (I)

Andreassi et al. clearly demonstrated that despite the fact that aclarubicin and doxorubicin share closely related structures, neither doxorubicin (tested at various concentrations) nor any other tetracycline derivatives tested showed any activity on the splicing of the SMN2 gene.

5) Unpredictability of the art. The art is highly unpredictable. The use of modified tetracycline compounds for uses other than antibiotics is growing, but the art reveals how these compounds react differently between in vitro and in vivo settings, as well as tissue-to-tissue variability, and have high degrees of variability in serum levels and half-lives. The art teaches that this variability is due to the structure of the tetracycline compound, but also to unknown *in vivo* environments which affect the tetracycline compound. The art also shows that antibiotic treatment for muscular dystrophy is not a reproducible or reliable alternative. Moreover, as stated above, Andreassi et al. clearly demonstrated the unpredictability associated with the administration of various tetracycline derivatives for the treatment of SMA. Although Aclarubicin is similar in structure to the genus of tetracycline derivatives encompassed by the instant claims, Aclarubicin is clearly not encompassed by the general formula (I) of the instant claims, thus it is structurally distinct from the compounds of the instant application. Although

Aclarubicin is known for its modulation of the splicing of the SMN gene associated with SMA, there is no guidance in the specification as filed or in the prior art of record that would allow the skilled artisan to utilize the compounds of the present invention in the treatment of SMA.

Applicants have not taught one of skill in the art how to decipher which of the thousands of tetracycline derivatives in the instant specification would be able to overcome known obstacles in the art. Applicant's have not shown any in vivo data to investigate the cellular uptake, half-life, clearance, etc. of the thousands of compounds disclosed, not how to address these issues, other than altering the effective amount based on compound, and size and weight of the subject. A skilled artisan would therefore be required to determine how each of the thousands of tetracycline compounds reacts *in vivo* in order to determine which one to even begin testing for a particular DTMR. Applicants have not disclosed how to treat individual DTMRs associated with splicing, particularly SMA, either *in vitro* or *in vivo*. Applicants have not addressed the differences associated with treating a DTMR not associated with splicing from one that is associated with splicing. The skilled artisan would therefore be forced to conduct undue trial and error in order to practice the claimed invention, depending on which DTMR, which subject, and which tetracycline compound derivative was being utilized for treating the subject.

6) Level of skill in the art. The level of skill is high. The invention as claimed reads on a method of treating any subject, including animals, and humans. There is no teaching on how to adjust the method between different subjects. There is no teaching

of how to decipher which tetracycline compounds are to be used for specific DTMRs associated with splicing, but not to be used for other DTMRs (with or without splicing). Applicant's disclose thousands of tetracycline compounds, but only show 1 single example of RNA modulation in two murine macrophage cell lines after exposure to two tetracycline compounds. Applicants do not disclose what genes are actually altered, nor if that alteration results in a modulation of proteins. Applicants teach that the only factors needed to determine "effective amount" is size and weight of the subject, and the choice of tetracycline compound, but does not teach how one of skill in the art would choose one derivative disclosed over another out of the thousands disclosed in the specification. Applicant does not address known obstacles in the art regarding the administration of different tetracycline compounds. The skilled artisan would therefore be forced to conduct undue trial and error in order to practice the claimed invention, depending on which DTMR associated with splicing, which subject, and which tetracycline compound derivative was being utilized for treating the subject.

7) The breadth of the claims. The breadth of the claims is broad. The invention as claimed reads on a method of treating any subject, including animals, and humans, using any one of the myriad of tetracycline compounds encompassed within formula (I) for treatment of a disease state associated with a DTMR associated with splicing, specifically for the treatment of SMA.

Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, including the highly unpredictable art, the scarcity of working examples provided by applicant, the lack of

guidance by the applicant, and the broad nature of the invention it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

Response to Arguments

13. Applicant's arguments filed 11/05/07 have been fully considered but they are not persuasive. Applicants traverse the 112 1st enablement rejection of the instant claims. Applicants argue that the specification is enabling with the general synthetic methods described in the specification and the examples, which describe the synthesis or examples of the compound. Specifically, Applicants argued the following, see page 111 of Applicant's reply filed 03/03/2009:

"[T]he instant specification describes several ways in which the modulation of RNA can occur. (See e.g., page 3, line 25 through page 7 line 28 of the specification as originally filed.).Moreover, Applicants submit that the evaluation of the effect of various tetracycline compounds on an SMA disease state is within the routine knowledge of a skilled artisan. For example, the modulation of RNA is described in the specification by direct or indirect binding (see e.g., page 7, line 29 through page 8, line 3), by altering RNA transcription (see e.g., page 4, lines 22-33), by altering RNA translation (see e.g., page 5, lines 4-14), by altering the half-life of RNA (see e.g., page 5, line 33 through page 6, line 5), by altering the translocation of RNA (see e.g., page 6, lines 15-24), and/or by altering the interactions of proteins with RNA (see e.g., page 7, line 22 through page 8, line 22). Methods for the detection of RNA modulation are also described in the specification. (See e.g., page 8, lines 23-26).

Furthermore, the gene modulated in the claimed treatment of SMA is the survival of motor neuron gene (SMN), as described in the incorporated references Philips et al. (2000), Cell. Mol. Life Sci., 57:235-249 and Stoss et al., (2000), Gene Ther. Mol. Biol. 5:9-30 (courtesy copies attached).

Likewise, Applicants have also described methods for identifying tetracycline compounds for treating a specific DTMR, such as SMA, as presently claimed. (See e.g., page 11, lines 8-19 of the specification as originally filed). Such methods include measuring the ability of a tetracycline compound to modulate RNA using any of the methods described above and comparing experimental results for a number of tetracycline compounds to identify those having superior properties for the treatment of

SMA. A skilled artisan would be able to routinely screen multiple tetracycline compounds to determine the best candidate(s) for the treatment of SMA."

Applicants have essentially argued that the disclosure of the SMN gene in Stoss et al. and Phillips et al., and the disclosure of generic methods for identifying compounds for treating a specific DTMR, such as SMA are sufficient to enable the full scope of the claimed invention by routine experimentation.

14. The examiner is respectfully not persuaded. In light of the analysis above, the examiner maintains that the art shows that treatment with tetracycline derivatives as therapeutics other than as antibiotics is not routine, as evidenced by Liu et al (see above), that diseases such as muscular dystrophy that have been treated with antibiotics have had irreproducible results as evidenced by Chakkalakal (see above) and Hertweck teaches that tetracycline derivatives are capable of inhibiting splicing, which taken together suggest that the single administration of tetracycline derivatives to treat any DTMR associated with splicing is not routine. Moreover, in regards to Andreassi et al., the art clearly demonstrates that there is a significant level of unpredictability associated with the administration of a tetracycline derivative and the treatment of specifically SMA, see for example Figure 1(A), page 2843).

15. Taking the state of the art, the unpredictability of the state of the art in regard to specific DTMR associated with splicing listed in the claims, added to the fact that applicant's disclose thousands of possible tetracycline derivatives, and argue that any one of them can be used to treat any single DTMR associated with splicing, but in fact do not disclose a single working example of treating a DTMR associated with splicing,

and as applicant's themselves admit, the teachings of the specification are "generic" and thus not specific for treating a DTMR associated with splicing, the examiner maintains that the skilled artisan would be forced to perform undue experimentation in order to make and use the claimed invention. Applicant's arguments that the specification provides assays for measuring RNA splicing are irrelevant, as the specification does not disclose how splicing is supposed to be modulated for any DTMR associated with splicing. Thus the skilled artisan would not be able to recognize if a change of splicing was a "treatment" as there is no disclosure of successful splicing modulation, or any teaching of what it ought to be in different disease states. ***Thus this rejection is maintained.***

16. Applicant's arguments with respect to claims 1, 36-47, 54, 57-64 under 35 USC 112, 1st ¶ for failing to comply to the written description requirement, have been considered but are moot in view of the new ground(s) of rejection.

17. Claims 1, 37-47, 54, 57, 59-60, and 62-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***(New Matter)***

18. Applicants claim a method for treating a Disease Treatable by Modulation of RNA (DTMR) associated with splicing of nuclear RNA, comprising: administering to said subject an effective amount of a tetracycline compound of formula (I) to modulate

splicing, wherein said DTMR associated with splicing of nuclear RNA is spinal muscular atrophy. .

19. Applicant's amendment to the claims to include the limitation "spinal muscular atrophy," however there is no mention of the limitation "spinal muscular atrophy," in the text of the specification as filed.

20. According to Applicants support for this limitation was found "for example, on pages 240-241 of Philips et al. (2000), Cell. Mol. Life Sci., 57:235-249 and on page 21 of Stoss et al, (2000), Gene Ther. Mol. Biol. 5:9-30 (courtesy copies enclosed), each of which is expressly incorporated by reference in the instant specification on page 9, lines 14-17 and lines 28-29 and page 102, lines 14-16 of the specification."

21. However, since it is clear that the term "spinal muscular atrophy," as taken from the disclosure of the Phillips et al. and Stoss et al. references, is relied upon to provide a written description of the claimed method (see Applicant's reply page 113), Applicant's reliance upon non-patent literature reference for the incorporation of "essential material" is improper and is therefore considered new matter, see 37 CFR 1.57(C), which states the following:

37 CFR 1.57(c) as set forth below:

> c) "Essential material" may be incorporated by reference, but only by way of incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. "Essential material" is material that is necessary to:
>
> (1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of 35 U.S.C. 112;

22. Moreover, there is no mention in the specification as filed, or in the disclosure of either Stoss et al. or Phillips et al. of a method of treating SMA comprising modulating nuclear RNA splicing by activation of cryptic splice sites, silencing of consensus splice sites, silencing of exonic or intronic splicing enhancers (ESEs or ISEs), silencing of exonic or inronic splicing silencers (ESSs or ISSs), alteration of the binding or a component of the splicing machinery to the RNA, or the affecting of intermolecular interactions between components of the splicing machinery, on any subject comprising administering an “effective amount" of the tetracycline compound of formula (I).

23. The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention.

24. In the instant case, applicants provide ample examples of making different tetracycline compounds (see examples 1-2), but do not, in fact, provide any data providing evidence for the in vivo treatment of SMA wherein an “effective amount" of the tetracycline compounds of the present invention are administered.

25. The skilled artisan would, without further undue experimentation would be unable to describe, or envision, a method for treating any subject having SMA comprising

administering an effective amount of any generic tetracycline compound disclosed in the claims. The skilled artisan would therefore conclude that the applicants have not fully reduced to practice the claimed invention, and thus were not in full possession of the claimed invention at the time of filing of the instant invention.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633